Nephrocalcinosis and urolithiasis in children

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Correction to: *Kidney International* (2011) **80**:1278–1291; doi:10.1038/ki.2011.336

In the above-cited article, Table 2 was published with incorrect alignment of age ranges and erroneous unit changes concerning the cystine and urate excretion levels. The urate gram units needed to be multiplied by 10.

In Table 1, the diagnosis related to *NPT2a* mutations should read 'Urolithiasis, osteoporosis, and persistent hypophosphatemia', and the fifth heading should read 'Hypouricemia' instead of 'Hypouricosuria'.

In addition, we would like to amend the recently unraveled sensitivity to vitamin D caused by *CYP24A1* mutations and characterized by symptomatic infantile hypercalcemia, hypercalciuria, and nephrocalcinosis to Table 2, which can be of utmost importance to clinicians.[1]

Please see below the corrected Tables 1 and 2.

1. Schlingmann KP, Kaufmann M, Weber S *et al.* Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *NEJM* 2011; **365**: 410–421.

Table 1 | Genetic diseases with urolithiasis and/or nephrocalcinosis according to the underlying metabolic derangement

Entity/disorder	Gene/gene product/locus	Inheritance	Hints and hallmarks
Hypercalciuria			
Autosomal dominant hypocalcemic hypercalciuria (ADHH)[48]	*CASR*/CaSR, 3q21.1 Gain-of-function mutations, usually private mutations, leading to leftward shift of extracellular calcium dose–response curve	**ad**	Mild, usually asymptomatic hypocalcemia, hypercalciuria, with elevated serum phosphate and low serum magnesium levels, PTH in the low normal range *nota bene:* vitamin D substitution will result in excess hypercalciuria, leading to NC, UL, and eventually CRF Note: inactivating mutations of CaSR increase the threshold for negative feedback and cause hypocalciuric hypercalcemia
Hypercalcemia with hypercalciuria[169] - familial isolated hyperparathyroidism (FIHP)	Menin, 11q13 Parafibromin, 1q31.3 CaSR, 3q21.1	**ad**	Familial isolated parathyroid tumors, inactivating mutations in CaSR
Idiopathic hypercalciuria[170–172]	*SAC*/soluble adenyl cyclase, 1q23.3–q24; sequence variations but no causative mutations	**ad**	Associated with absorptive type of hypercalciuria, normocalcemia, normal PTH levels, low bone mineral density
	VDR/vitamin D receptor, 12q12–q14, polymorphisms, but no causative mutations	**ad**	Associated with resorptive type of hypercalciuria
	Gene remains to be found, 9q33.2–q34.2 locus	**ad**	Autosomal dominant nephrolithiasis
Bartter syndromes (BS)[169]			
Type 1	*SLC12A1*/NKCC2 (bumetanide-sodium-potassium-chloride cotransporter); 15q15–q21.1	**ar**	Classical BS: hypokalemic alkalosis, renal salt wasting, hyperreninemic hyperaldosteronism, hyperprostaglandinemia, hypercalciuria and NC, potential CRF Antenatal BS (polyhydramnios, salt wasting, prematurity, volume depletion)
Type 2	*KCNJ*/ROMK (renal outer-medullary potassium channel); 11q24	**ar**	Classical/antenatal BS, hypercalciuria and NC Transient neonatal hyperkalemia later evolving into (modest) hypokalemia, potential CRF
Type 3	*CLCNKB*/CLC-Kb (voltage-gated chloride channel); 1q36	**ar**	Mostly classical BS, wide phenotype variation (diagnosis neonatal period to adulthood), less hypercalciuria and NC, potential CRF
Type 4	*BSND*/Barttin; 1q31	**ar**	Usually severe antenatal BS with sensorineuronal deafness but less hypercalciuria and NC, CRF
Type 5	*CASR*/CaSR, (severe gain-of-function mutations); 3q21.1	**ad**	Early (symptomatic) hypocalcemia and hypercalciuria with NC (see above) followed later by classical BS features
Dent's disease			
Dent 1 (ref. 53)	*CLCN5* chloride/proton antiporter CLC5; Xp11.22 (Dent 1), mutations in 60% of cases	**Xr**	Male gender, FS (aminoaciduria, phosphaturia, glycosuria, kaliuresis, impaired acidification), LMW proteinuria, hypercalciuria (less severe with age), NC/UL, CRF regular
Dent 2 (ref. 173)	*OCRL1* (Dent 2), mutations in 15% of cases	**Xr**	Patients with *OCRL1* mutation and Dent's disease lack cataracts (BS like phenotype termed BS type 6 was reported in a single turkish patient with *CLCN5* mutation)
Lowe's (oculorenocerebral) syndrome[174]	*OCRL1*/phosphatidylinositol-4,5-biphosphate-5-phosphatase ocrl1; Xq25	**Xr**	Male gender, congenital cataracts, mental retardation, hypotonia, rickets, proximal tubular defect (bicarbonate, phosphate, aminoaciduria), nephrotic range proteinuria, metabolic acidosis, hypercalciuria and NC/UL, CRF regular
Urolithiasis, osteoporosis, and persistent hypophosphatemia[175]	*NPT2a*/sodium-phosphate-cotransporter type 2a (SLC34A1); 5q35	**ad**	Excess urinary phosphate excretion, hypophosphatemia, elevated 1,25OH vitamin-D, elevated AP, suppressed PTH, hypercalcemia and hypercalciuria
Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)[176]	*NPT2c*/sodium-phosphate-cotransporter type 2c (SLC34A3); 9q34	**ar**	Excess loss of urinary phosphate, hypophosphatemia, severe rickets, hypercalciuria but no hypercalcemia, UL
Williams–Beuren syndrome[177]	Continuous gene deletion syndrome (1.55 Mb including *ELN*, *LIMK1*, *RFC2*); 7q11.23	**Mostly sporadic**	Multisystemic developmental disorder with mental retardation, distinctive neuropsychological profile 'happy party manner', variable cardiovascular findings (aortic stenosis), abnormalities of renal tract and connective tissue, temporary hypercalcemia and hypercalciuria, NC/UL

Table 1 | Continued

Entity/disorder	Gene/gene product/locus	Inheritance	Hints and hallmarks
Vitamin D-induced infantile hypercalcemia, hypercalciuria and nephrocalcinosis (formerly known as idiopathic non-syndromal infantile hypercalcemia or Lightwood type)	*CYP24A1*/25 hydroxy vitamin D24-hydroxylase, the key mitochondrial protein for degradation of 1,25-dihydroxyvitamin D3, the physiologically active form of vitamin D3*; 20q13.2*	**ar**	Increased sensitivity to regular (supplemental) doses of vitamin D resulting in severe symptomatic hypercalcemia (failure to thrive, hypotonia, dehydration) with hypercalciuria and nephrocalcinosis There might be a wide phenotypic spectrum associated with *CYP24A1* mutations and incomplete penetrance Patients usually demonstrate low/suppressed intact PTH levels and 1,25 dihydroxy-vitamin D3 levels at the upper normal limit
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)[178]	*CLDN16*/claudin 16/paracellin 1; 3q27	**ar**	Symptomatic hypomagnesemia and hypocalcemia, hypercalciuria and NC/UL, d-RTA, regular CRF
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular involvement[179]	*CLDN19*/claudin 19; 1p34.2	**ar**	Hallmarks of FHHNC with multiple ocular abnormalities
Wilson's disease[14]	*ATP7B*/copper transporting ATPase 2; 13q14.3	**ar**	Fanconi syndrome, liver dysfunction, neurologic symptoms, Kayser–Fleischer cornea ring, elevated urinary copper excretion reduced coeruloplasmin, hypercalciuria, UL, NC, CRF
Tyrosinemia type 1 (ref. 14)	*FAH*/fumarylacetone-acetate hydrolase; 15q.23–q25	**ar**	Fanconi syndrome, rickets, liver failure, coagulopathy, hypercalciuria, UL, NC, CRF
Liddle's syndrome (pseudo-hyperaldosteronism type 1)[14]	*SCNN1B* and *SCNN1G*/beta and gamma subunits of epithelial sodium channel (ENaC); 16p12	**ad**	Rare, triad of hypokalemia, alkalosis and sodium-sensitive hypertension, suppressed aldosterone levels, hypercalciuria and NC, risk of CRF, treatment with amiloride (ENaC blocker)
Gordon's syndrome (pseudo-hypoaldosteronism type 2)[14]	*WNK1* 12p13.3, *WNK4* 17q21.31/serine-threonine kinase	**ad**	Hyperkalemia, metabolic acidosis (reduced ammonium excretion), hypertension and hypercalciuria (RTA type 4)
Hyperoxaluria			
Primary hyperoxalurias			
Primary hyperoxaluria type I (PH I)[76]	*AGXT*/alanin-glyoxylate-aminotransferase (AGT); 2q37.3 80–90% of PH cases	**ar**	Recurrent UL and/or progressive NC, UTI, severe hyperoxaluria (>1 mmol per 1.73 m^2 per day), hyperglycolic aciduria, ESRF regular outcome (neonatal period to late adulthood), systemic oxalate deposition with advanced renal failure leads to a multisystemic disease character
Primary hyperoaxluria type II (PH II)[81]	*GRHPR*/glyoxylate reductase/hydroxylpyruvate reductase (GRHPR) 9q11, 10% of PH cases	**ar**	Hallmarks recurrent UL, NC less frequent, hyperoxaluria plus marked L-glyceric aciduria in most cases, lower (about 20%) risk of ESRF
Primary hyperoaxluria type III (PH III)[84]	*DHDPSL*/4-hydroxy-2-oxoglutarate aldolase 10q24.2	**ar**	Likely the second most frequent PH type Disease seems to remit with age No case of ESRF reported (*nota bene*: very limited data)
Atypical PH	Unknown, negative *AGXT*, *GRHPR*, and *DHDPSL* mutational analysis		Hyperoxaluria and clinical features overlapping with PH type I–III Risk of ESRF not defined
Cystinuria			
Cystinuria type I (heterocygotes are silent)[181]	*SLC3A1*/rBAT; 2p16.3, causative mutations result mostly in type I	**ar**	Impaired renal transport of cystine and dibasic amino acids, high urinary cystine levels
Cystinuria type II (heterocygotes show a variable degree of hypercystinuria)[181]	*SLC7A9*/b0,+ AT; 19q13.1, causative mutations may result in type I phenotype	**adip**	
Mixed type I/II cystinuria phenotype[181]	All genotypes possible but mostly *SLC7A9* mutations		

Table 1 | Continued

Entity/disorder	Gene/gene product/locus	Inheritance	Hints and hallmarks
Hyperuricosuria			
Lesch–Nyhan syndrome[182]	HPRT/hypoxanthine-guanine-phosphoribosyl-transferase; Xq26	Xr	Symptomatic in males, normal at birth followed by progressive psychomotor delay, gout, hyperuricosuria, recurrent UL, automutilation
Partial HPRT deficiency[182]			Hyperuricosuria, wide spectrum of symptoms with asymptomatic course in less severe forms
Glycogenosis type 1a (ref. 180)	*G6PC*/glucose-6-phosphatase; 17q21	ar	Episodic severe hypoglycemic, lactic acedemia, hyperuricosuria, hypercalciuria, hypocitraturia, recurrent UL, NC, Fanconi syndrome, FSGS, renal amyloidosis, CRF
Hypouricemia			
APRT deficiency[183]	*APRT*/adenine phosphoribosyl transferase; 16q24.3	ar	Urinary accumulation of the insoluble purine 2,8 dihydroxyadenine (round + brown crystals), UL, CRF
Xanthinuria[109]	XDH/xanthine dihydrogenase oxidase; 2p22 (type 1) Type 2 dual deficiency of XDH plus aldehyde oxidase	ar	Noticeable low levels of uric acid in serum and urine, xanthinuria, UL (radiotransparent)
Urate transporter 1 (ref. 184)	SLC22A12/renal urate anion exchanger URAT1; 11q13	ar	Sporadic/familial renal hypouricemia, UL, and risk of exercise induced ARF
Renal tubular acidosis (RTA) hypocitraturia + hypercalciuria			
RTA (54,185,186)			
Renal tubular acidosis type 1	*ATP6V1/*B1 subunit of H+ ATPase; 2cen-q13	ar	Distal RTA, metabolic acidosis (impaired H+ excretion) of early onset with early NC and hearing loss, hypocitraturia, hypercalciuria, UL, NC, hypokalemia, rickets, failure to thrive
	*ATPV0A4/*A4 subunit of H+ ATPase 7q33–34	ar	Later onset of sensorineural deafness (sometimes normal hearing)
	*SLC4A1/*basolateral Cl/HCO3 exchanger AE1; 17q21–22	ad	Distal RTA of later onset, milder metabolic acidosis, urine pH >6.1, hypokalemia, hypocitraturia, hypercalciuria, UL, NC, sometimes rickets
	*SLC4A1/*basolateral Cl/HCO3 exchanger AE1; 17q21–22	ar	Distal RTA of childhood onset, metabolic acidosis plus hemolytic anemia in southeast Asians
Renal tubular acidosis type 2	*SLC4A4/*NBC1 sodium bicarbonate cotransporter; 4q21	ar	Proximal RTA, (milder) metabolic acidosis by bicarbonate wasting, hypokalemia, growth retardation, ocular abnormalities, enamel defects, intellectual impairment, less severe hypercalciuria and hypocitraturia
Renal tubular acidosis type 3 (mixed type)	*CA2/carboanhydrase 2*	ar	Bicarbonate wasting + inability to acidify the urine: RTA plus osteopetrosis (Guibaud Vainsel syndrome), intracerebral calcification, growth failure, intellectual impairment, conductive deafness

Abbreviations: ad, autosomal dominant; adip, autosomal dominant with incomplete penetrance; ap, alkaline phosphatase; ar, autosomal recessive; ARF, acute renal failure; CaSR, calcium-sensing receptor; CRF, chronic renal failure; ESRF, end-stage renal failure; FS, Fanconi syndrome; FSGS, focal segmental glomerulosclerosis; LMW, low-molecular-weight proteinuria; PTH, parathyroid hormone; NC, nephrocalcinosis; UL, urolithiasis; Xr, x-linked recessive. References are imbedded in table.

Table 2 | Normal values for lithogenic and stone-inhibitory parameters in spot urine (related to creatinine excretion) and 24-h urine collection (tubes or containers need to be preserved with either thymol 5% in isopropanol, or 2 N HCl before collection starts)

Soluble/creatinine ratio (spot urine samples)

Calcium/creatinine			Citrate/creatinine			Cystine/creatinine			Oxalate/creatinine			Urate/creatinine		
	mol/mol	g/g		mol/mol	g/g		mmol/mol	mg/g		mmol/mol	mg/g		mol/mol	g/g
<12 Months	<2.2	<0.8	0–5 Years	>0.12 to 0.25	>0.2 to 0.42	<1 Month	<85	<180	0–6 Months	<325 to 360	<260 to 88	<12 Months	<1.5	<2.2
1–3 Years	<1.5	<0.53							7–24 Months	<132 to 174	<110 to 39	1–3 Years	<1.3	<1.9
3–5 Years	<1.1	<0.4				1–6 Months	<53	<112	2–5 Years	<98 to 101	<80 to 81	3–5 Years	<1.0	<1.5
5–7 Years	<0.8	<0.3	>5 Years	>0.08 to 0.15	>0.14 to 0.25				5–14 Years	<70 to 82	<60 to 65	5–10 Years	<0.6	<0.9
>7 Years	<0.6	<0.21				>6 Months	<18	<38	>14 Years	<40	<32	>10 Years	<0.4	<0.6

Urinary excretion of soluble in 24-hour urine samples

Calcium excretion		Citrate excretion		Cystine excretion		Oxalate excretion		Urate exretion	
All age groups	<0.1 mmol/kg per 24 h <4 mg/kg per 24 h	All age groups	*Boys*: >1.9 mmol per 1.73 m^2 per 24 h >365 mg per 1.73 m^2 per 24 h *Girls*: >1.6 mmol per 1.73 m^2 per 24 h >310 mg per 1.73 m^2 per 24 h	<10 Years >10 Years	<55 μmol per 1.73 m^2 per 24 h <13 mg per 1.73 m^2 per 24 h <200 μmol per 1.73 m^2 per 24 h <48 mg per 1.73 m^2 per 24 h	All age groups	<0.5 mmol per 1.73 m^2 per 24 h <45 mg per 1.73 m^2 per 24 h	<1 Year 1–5 Years >5 Years	<70 μmol/kg per 24 h <**13** mg/kg per 24 h <65 μmol/kg per 24 h <**11** mg/kg per 24 h <55 μmol/kg per 24 h <**9** mg/kg per 24 h

Repeat collection after stone passage or removal, as stones *in situ* may diminish lithogenic excretion parameters. Check 24-h urine volume and creatinine excretion (2 mg/kg ± 0.8 mg) to ensure adequate collection.